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Health and Environmental Effects Profile for Maleic Anhydride

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16. ABSTRACT

The Health and Environmental Effects Profile for Maleic Anhydride was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Maleic anhydride has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for maleic anhydride is 0.10 mg/kg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for maleic anhydride is 100.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR MALEIC ANHYDRIDE

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3112. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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EXECUTIVE SUMMARY

Maleic anhydride is a chemically reactive compound produced in the United States in large commercial quantities. In 1984, 359 million pounds were produced (USITC, 1985) by five U.S. manufacturers having a combined annual capacity of 470 million pounds (SRI, 1985). Maleic anhydride is used in the synthesis of resins, copolymers, lube oil additives, pesticides and other organic compounds (CMR, 1983; Robinson and Mount, 1981).

Maleic anhydride is expected to be a short-lived chemical in the ambient environment because of its chemical reactivity. In water, hydrolysis is the dominant fate process; maleic anhydride hydrolyzes rapidly to maleic acid with a half-life of 3.3 minutes at 0°C and a half-life of 38 seconds at 18.55°C (Bunton et al., 1963). Solutions of maleic anhydride have been shown to be susceptible to significant biodegradation in various BOD and activated sludge tests (Takemoto et al., 1981; Heukelekian and Rand, 1955; Matsui et al., 1975); however, these tests may actually be measuring the biodegradation of maleic acid formed by hydrolysis. Maleic acid/maleic anhydride are normally easily biodegradable by biological sewage treatment (Thom and Agg, 1975).

Theoretically calculated rate constants for the atmospheric reaction between maleic anhydride and OH radicals or ozone (Cupitt, 1980) indicate that maleic anhydride will be rapidly removed from the atmosphere by these molecules. The calculated half-lives for these reactions in a typical atmosphere are 3.2 and 1.2 hours for OH radical and ozone, respectively. Atmospheric photolysis and physical removal are possible (Cupitt, 1980); however, dissolution into clouds and rainwater is expected to result in the hydrolysis of maleic anhydride. Maleic anhydride is also expected to

hydrolyze in moist soil. While the high water solubility of maleic anhydride predicts that it will leach easily in soil, the significance of leaching should be minimized by concurrent hydrolysis. Photolysis and evaporation from soil surfaces are possible.

A lack of monitoring data for maleic anhydride in the ambient aquatic or atmospheric environments is consistent with its rapid degradation that is due to hydrolysis or reaction with OH radicals and ozone. Sources of atmospheric emissions include phthalic anhydride production (where maleic anhydride is formed as a by-product), maleic anhydride production and endproduct manufacture (Patterson et al., 1976; Pervier et al., 1974; Moores, 1975). Maleic anhydride has been detected in cigarette smoke (Schumacher et al., 1977) and in the aroma of black tea (Mick and Schreier, 1984).

The limited information available indicates that maleic anhydride is acutely toxic to fish and aquatic invertebrates at concentrations of $\geq$56 mg/ℓ. LC_{50} values for fish range from 75 mg/ℓ for bluegills and rainbow trout to 240 mg/ℓ for mosquitofish (Cohle and McAllister, 1982a,b; Turnbull et al., 1954; Wallen et al., 1957). The EC_{50} for immobilization of Daphnia magna is 88 mg/ℓ (Bringmann and Kuehn, 1982). No toxic effects were reported in any species at concentrations <50 mg/ℓ. Pertinent data regarding the chronic toxicity or accumulation of maleic anhydride in aquatic organisms could not be located in the available literature as cited in the Appendix.

Braun et al. (1975) determined an uptake rate constant (k_a) of 3.49×10^{-3} $days^{-1}$ and an elimination rate constant (k_e) of 8.32×10^{-2} $days^{-1}$ for dogs treated orally with 60 mg/kg/day for 90 days using a nonlinear parameter estimation program and assuming a one-compartment model.

The model predicted that steady-state was reached by day 55. Degradation of maleic anhydride would involve hydrolysis to maleic acid (U.S. EPA, n.d.), which may be hydroxylated to malic acid (U.S. EPA, 1981). Malic acid may then enter the tricarboxylic acid cycle or be excreted unchanged or in conjugated form (U.S. EPA, 1981).

The carcinogenicity of maleic anhydride has not been adequately tested nor has it been scheduled for testing by the National Toxicology Program (NTP, 1986). Preache (1983) observed no treatment-related increase in tumorigenesis in rats given dietary maleic anhydride at concentrations providing doses of 0, 10, 32 and 100 mg/kg/day for 2 years. Inadequate evidence of carcinogenicity was provided by Dickens and Jones (1963) who observed local fibrosarcomas in rats subcutaneously injected with maleic anhydride. Maleic anhydride was positive in the chromosomal aberration test in Chinese hamster cells without activation, but negative for chromosome aberrations in the bone marrow of rats exposed by inhalation (Farrow and Cortina, 1983) and negative in the Salmonella typhimurium reverse mutation test with and without metabolic activation (Ishidate and Yoshikawa, 1980; Ishidate et al., 1981). The teratogenicity of maleic anhydride has not been adequately tested by relevant routes; in mice, an intraperitoneal dose of 36.8 mg/kg on days 11-13 of gestation appeared to be a threshold associated with malformation in the offspring (Dixon et al., 1978; Brown et al., 1978). No effects on reproductive indices were observed in rats treated by gavage with 20, 55 or 150 mg/kg/day for three generations (Jessup et al., 1982).

The chronic toxicity of maleic anhydride has not been adequately studied. Preache (1983) fed rats diets providing doses of 0, 10, 32 or 100 mg/kg/day.

At 32 and 100 mg/kg/day, male rats had a dose-related, but slight (<6%) decrease in body weights, which was statistically significant. A marginal decrease in body weight accompanied by decreased food consumption was also observed in female rats at 32 and 100 mg/kg/day. Since decreased food consumption was also reported at sporadic intervals in these groups, the biological significance of these observations is questionable. Because the maleic anhydride in the stored feed hydrolyzed to maleic acid, the doses were probably overestimated. In the 3-generation study, compound-related mortality and renal pathology occurred in F_0 and F_1 parent rats treated by gavage with 150 mg/kg/day (Jessup et al., 1982). In rats that survived until sacrifice, renal lesions occurred randomly in F_0 rats treated at 20, 55 and 150 mg/kg/day and were considered compound-related.

In subchronic feeding studies, no effects were observed in rats given $\leq$40 mg/kg/day for 90 days (Humiston et al., 1975a). At $\geq$100 mg/kg/day, there were gross and histopathological renal lesions, at $\geq$250 mg/kg/day, increased kidney weights and at 600 mg/kg/day, increased liver weights and proteinuria. The only effects in dogs given 20, 40 or 60 mg/kg/day in the diet for 90 days were equivocal decreases in packed cell volume and hemoglobin concentration of male dogs receiving 60 mg/kg/day (Humiston et al., 1975b). Acute oral LD_{50} values range from 390-875 mg/kg in guinea pigs, mice, rats and rabbits (Marhold, 1977; Berzins, 1967).

Inhalation exposure to maleic anhydride vapor at 0.0011, 0.0033 and 0.010 mg/ℓ, 6 hours/day, 5 days/week for 6 months resulted in dose-related increased severity of nasal and ocular irritation in rats and hamsters at all concentrations and monkeys at the high concentration (Ulrich et al., 1981). Rats at 0.0033 and 0.01 mg/ℓ also had reduced body weights. In

rats exposed by inhalation to ≥0.012 mg/ℓ, 6 hours/day, 5 days/week for 4 weeks, upper respiratory and lung squamous metaplasia, inflammatory infiltrate, hyperplasia and hemorrhage were observed (Goldenthal et al., 1979b).

Occupational exposure of humans to maleic anhydride has been associated with sensitization dermatitis, chronic bronchitis, asthma, pulmonary edema, upper respiratory tract irritation and corneal burns (U.S. EPA, 1981; Grigor'yeva, 1966; ACGIH, 1986). Exposures to 1.0-8.0 mg/m³ for 15 minutes may cause eye irritation and continued exposure may result in chronic eye irritation and keratitis (ACGIH, 1986).

An ADI of 0.10 mg/kg/day or 7.0 mg/kg for a 70 kg human was derived from the NOAEL of 10 mg/kg/day in the 2-year dietary study in rats by Preache (1983), using an uncertainty factor of 100. An RQ of 100 was derived based on the upper respiratory tract lesions observed in rats exposed by inhalation to ≥0.012 mg/ℓ 6 hours/day, 5 days/week in the study reported by Goldenthal et al. (1979b). Maleic anhydride is an IARC Group 3 and a CAG Group D chemical, indicating that data regarding the carcinogenicity of maleic anhydride to rats are inadequate.

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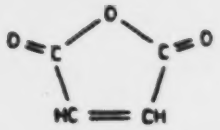
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
ATP	Adenosine triphosphate
BOD	Biochemical oxygen demand
bw	Body weight
CAS	Chemical Abstracts Service
CS	Composite score
EC_{50}	Concentration effective to 50% of recipients (and all other subscripted concentration levels)
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dosage levels)
LD_{50}	Dose lethal to 50% of recipients (and all other subscripted dosage levels)
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
TLV	Threshold limit value
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Maleic anhydride is the common chemical name, but this compound is also known as 2,5-furandione, cis-butenedioic anhydride, toxilic anhydride, maleic acid anhydride and dihydro-2,5-dioxofuran. The structure, molecular weight, empirical formula and CAS Registry number for maleic anhydride are as follows:



Molecular weight: 98.06

Empirical formula: $C_4H_2O_3$

CAS Registry number: 108-31-6

1.2. PHYSICAL AND CHEMICAL PROPERTIES

At room temperature, maleic anhydride is a colorless to white solid that forms orthorhombic crystals (Windholz, 1983; Hawley, 1977). It is soluble in water but decomposes to form maleic acid. Maleic anhydride is soluble in acetone, ether, chloroform, benzene, toluene, xylene or ethyl acetate; it is soluble in alcohols with ester formation (Windholz, 1983; Hawley, 1977). Selected physical properties are listed below:

Melting point:	52.85°C	Robinson and Mount, 1981
Boiling point:	202°C	Robinson and Mount, 1981
Specific gravity (20/20°C):	1.48	Robinson and Mount, 1981
Water solubility:		
at 25°C	163,000 ppm	U.S. EPA, 1985
at 30°C	163,000 ppm	Perry and Green, 1984

Vapor pressure:		
at 63.4°C	5 mm Hg	Perry and Green, 1984
at 44°C	1 mm Hg	Perry and Green, 1984
at 25°C	0.1 mm Hg	(Singh et al., 1984)
at 25°C	0.2 mm Hg	(extrapolated using Clausius-Clapeyron equation)
at 20°C	0.3 mm Hg (calculated)	Weber et al., 1981
Log K_{ow}:	not available	
Air odor threshold:	0.32 ppm	Amoore and Hautala, 1983
Air conversion factors:	1 mg/m³ = 0.25 ppm 1 ppm = 4.0 mg/m³	Verschueren, 1983

Maleic anhydride hydrolyzes in water to yield maleic acid (Bunton et al., 1963; Windholz, 1983). Both the ethylenic double bond and the carbonyl groups of maleic anhydride may participate in various chemical reactions (Robinson and Mount, 1981). The ability of maleic anhydride to undergo Diels-Alder reactions and copolymerizations is commercially important.

1.3. PRODUCTION DATA

Maleic anhydride was first offered for commercial sale in 1933 (Gardner and Flett, 1952). Production of maleic anhydride in the United States in 1983 and 1984 was reported to be 299 and 359 million pounds, respectively (USITC, 1984a, 1985). Imports through principal U.S. customs districts in 1983 was 5.6 million pounds (USITC, 1984b).

The U.S. manufacturers of maleic anhydride are listed in Table 1-1 along with their respective locations and annual capacities. Maleic anhydride is commercially manufactured by the vapor-phase oxidation of benzene or n-butane over a catalyst (Robinson and Mount, 1981); it can also be recovered as a by-product from phthalic anhydride production. In the United States, virtually all production is based on n-butane feedstock or is being converted to n-butane from benzene feedstock (SRI, 1985).

TABLE 1-1

United States Manufacturers of Maleic Anhydride*

Manufacturer	Location	Annual Capacity (millions of pounds)
Ashland Oil	Neal, WV	50
Denka Chem.	Houston, TX	50
Monsanto	Pensacola, FL	130
	St. Louis, MO	110
Standard Oil (Ind.) Amoco Chem.	Joliet, IL	60
U.S. Steel Corp.	Neville Island, PA	70
	Total	470

*Source: SRI, 1985

1.4. USE DATA

The end-use pattern for maleic anhydride is reported as follows (CMR, 1983):

Unsaturated polyester resins	52%
Lube oil additives	12%
Agricultural chemicals	9%
Fumaric acid	8%
Copolymers	6%
Malic acid	4%
Miscellaneous	7%
Exports	2%

The most important use is the formation of resins for use in boats, autos, trucks, buildings, tanks, piping and electrical goods (Robinson and Mount, 1981). Lube oil additives synthesized from maleic anhydride are used to prolong oil-change intervals and improve engine efficiency. Pesticides made from maleic anhydride include malathion, maleic hydrazide, captan, endothall, difolatan and alar (Robinson and Mount, 1981).

1.5. SUMMARY

Maleic anhydride is a chemically reactive compound produced in the United States in large commercial quantities. In 1984, 359 million pounds were produced (USITC, 1985) by five U.S. manufacturers having a combined annual capacity of 470 million pounds (SRI, 1985). Maleic anhydride is used in the synthesis of resins, copolymers, lube oil additives, pesticides and other organic compounds (CMR, 1983; Robinson and Mount, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.1.1. Hydrolysis. Bunton et al. (1963) experimentally measured the rate of hydrolysis of maleic anhydride in an initially neutral aqueous solution. The first-order rate constants at 0°C and 18.55°C were determined to be 3.48×10^{-3} and 1.83×10^{-2} sec^{-1}, respectively, which can be used to calculate respective half-lives of 3.3 minutes and 38 seconds. The hydrolysis product was maleic acid. These data clearly indicate that hydrolysis is the dominant environmental fate mechanism for maleic anhydride in aqueous solutions.

2.1.2. Oxidation and Photolysis. Pertinent data regarding the aquatic oxidation and photolysis of maleic anhydride could not be located in the available literature as cited in the Appendix; however, these fate mechanisms are unlikely to be important because of the rapid hydrolysis of maleic anhydride in water.

2.1.3. Microbial Degradation. Using both the standard dilution method and the seawater dilution method, Takemoto et al. (1981) measured 5-day BOD values for an aqueous solution initially containing 7 ppm maleic anhydride; BOD values of 68.9 and 74.0% of theoretical were determined, respectively.

Heukelekian and Rand (1955) reported the results of two 5-day BOD tests using maleic anhydride, a Warburg respirometer and a sewage seed. BOD values of 0.60 and 0.40 g/g were reported, which can be averaged to obtain a 51% BOD of theoretical.

Matsui et al. (1975) found 98-99% removal of maleic anhydride in an activated sludge system after a 4-hour period.

The BOD values determined in these studies do not consider the hydrolysis of maleic anhydride in water to yield maleic acid and are, therefore,

predominantly measuring the biodegradation of maleic acid. Thom and Agg (1975) reported that maleic acid/maleic anhydride are normally easily biodegradable by biological sewage treatment.

2.1.4. Volatilization. Volatilization of maleic anhydride from water is not expected to be significant because of its rapid hydrolysis. Also, assuming maleic anhydride did not hydrolyze or dissociate in water, the Henry's Law constant can be calculated from the vapor pressure (0.1 mm Hg) and water solubility (163,000 ppm) at 25°C to be 8×10^{-8} atm·m³/mol, indicating that maleic anhydride is essentially nonvolatile in water (Lyman et al., 1982).

2.1.5. Adsorption and Bioconcentration. The high water solubility of maleic anhydride suggests that adsorption to particulates and sediment in water, and bioaccumulation by aquatic organisms are not significant.

2.2. AIR

2.2.1. Chemical Removal Processes. The rate constant for the atmospheric reaction between maleic anhydride and OH radicals has been theoretically calculated to be 6.0×10^{-11} cm³/molecule-sec (Cupitt, 1980; Singh et al., 1984). Assuming a typical atmosphere contains 10^6 ·OH molecules/cm³, the half-life for this reaction is calculated to be 3.2 hours.

The rate constant for the atmospheric reaction between maleic anhydride and ozone has been theoretically calculated to be 1.6×10^{-16} cm³/molecule-sec (Cupitt, 1980). Assuming a typical atmosphere contains 10^{12} ozone molecules/cm³, the half-life for this reaction is calculated to be 1.2 hours.

Maleic anhydride absorbs UV radiation in the spectral region between 290 and 335 nm (Sadtler, 1961), which indicates that atmospheric photolysis is possible (Cupitt, 1980). Rate data are not available, however, to determine the relative significance of photolysis.

Rosenfeld and Murphy (1967) examined the hydrolysis of maleic anhydride on exposure to atmospheres of relative humidities of 96 and 50% at 22-23°C. At 96% relative humidity, hydrolysis of maleic anhydride to maleic acid was complete in 21 hours; however, no hydrolysis occurred at 50% relative humidity.

The anticipated products of the atmospheric degradation of maleic anhydride are carbon dioxide and carbon monoxide and acids, aldehydes and esters which should photolyze (Cupitt, 1980).

2.2.2. Physical Removal Processes. The physical removal of maleic anhydride from air is possible (Cupitt, 1980). Dissolution into clouds and rainwater, however, is expected to result in the hydrolysis of maleic anhydride.

2.3. SOIL

Because maleic anhydride hydrolyzes rapidly in water (Bunton et al., 1963), it is also expected to hydrolyze in moist soil. The high water solubility suggests that maleic anhydride will be highly mobile and easily leached in soil; however, the rapid hydrolysis of the compound in moist conditions should minimize the significance of leaching.

The vapor pressure (0.1 mm Hg at 25°C) of maleic anhydride suggests that evaporation from dry soil surfaces may occur. Also, the ability of maleic anhydride to absorb sunlight radiation (Sadtler, 1961) indicates a potential for soil surface photolysis. Pertinent data regarding the biodegradation of maleic anhydride in soil could not be located in the available literature as cited in the Appendix.

2.4. SUMMARY

Maleic anhydride is expected to be a short-lived chemical in the ambient environment because of its chemical reactivity. In water, hydrolysis is the

dominant fate process; maleic anhydride hydrolyzes rapidly to maleic acid with a half-life of 3.3 minutes at 0°C and a half-life of 38 seconds at 18.55°C (Bunton et al., 1963). Solutions of maleic anhydride have been shown to be susceptible to significant biodegradation in various BOD and activated sludge tests (Takemoto et al., 1981; Heukelekian and Rand, 1955; Matsui et al., 1975); however, these tests may actually be measuring the biodegradation of maleic acid formed by hydrolysis. Maleic acid/maleic anhydride are normally easily biodegradable by biological sewage treatment (Thom and Agg, 1975).

Theoretically calculated rate constants for the atmospheric reaction between maleic anhydride and OH radicals or ozone (Cupitt, 1980) indicate that maleic anhydride will be rapidly removed from the atmosphere by these molecules. The calculated half-lives for these reactions in a typical atmosphere are 3.2 and 1.2 hours for OH radical and ozone, respectively. Atmospheric photolysis and physical removal are possible (Cupitt, 1980); however, dissolution into clouds and rainwater is expected to result in the hydrolysis of maleic anhydride. Maleic anhydride is also expected to hydrolyze in moist soil. While the high water solubility of maleic anhydride predicts that it will leach easily in soil, the significance of leaching should be minimized by concurrent hydrolysis. Photolysis and evaporation from soil surfaces are possible.

3. EXPOSURE

3.1. WATER

The U.S. EPA STORET data base contains no postings for maleic anhydride. Other ambient aquatic monitoring data for maleic anhydride could not be located in the available literature as cited in the Appendix. This lack of monitoring detections is consistent with its rapid hydrolysis in water.

3.2. FOOD

Pertinent data regarding the detection of maleic anhydride in food could not be located in the available literature as cited in the Appendix; however, Mick and Schreier (1984) found that the aroma of black tea is a complex mixture of many organic compounds (which includes maleic anhydride), although this may be more pertinent to inhalation exposure than to food exposure.

3.3. INHALATION

Maleic anhydride is emitted to the atmosphere by process emissions from its manufacture (Pervier et al., 1974), by air emissions generated at phthalic anhydride plants that produce maleic anhydride as a by-product (Hughes and Jefcoat, 1979; Fawcett, 1970; Moores, 1975) and by end-product manufacture, which uses maleic anhydride. Patterson et al. (1976) suggested that the primary emission sources of maleic anhydride dust or vapor in descending order are phthalic anhydride production, maleic anhydride production, end-product manufacture and packaging losses.

The photochemical reaction between xylene or toluene with nitric oxide, air and UV radiation has been shown to produce maleic anhydride (Kato, 1981; Katou and Hanai, 1979), suggesting that maleic anhydride may form in the atmosphere during severe photochemical smog conditions.

Maleic anhydride has not been detected in the ambient atmosphere by various U.S. EPA and other monitoring studies (Brodzinsky and Singh, 1982), probably because of its rapid degradation by OH radicals and ozone. It has been detected in occupational air where it is manufactured and used (Hartle, 1980; Van Wagenen, 1984).

Maleic anhydride has been detected in cigarette smoke (Schumacher et al., 1977).

3.4. DERMAL

Pertinent data regarding dermal monitoring of maleic anhydride could not be located in the available literature as cited in the Appendix. Dermal exposure seems most likely in occupational settings.

3.5. SUMMARY

A lack of monitoring data for maleic anhydride in the ambient aquatic or atmospheric environments is consistent with its rapid degradation due to hydrolysis or reaction with OH radicals and ozone. Sources of atmospheric emissions include phthalic anhydride production (where maleic anhydride is formed as a by-product), maleic anhydride production and end-product manufacture (Patterson et al., 1976; Pervier et al., 1974; Moores, 1975). Maleic anhydride has been detected in cigarette smoke (Schumacher et al., 1977) and in the aroma of black tea (Mick and Schreier, 1984).

4. PHARMACOKINETICS

Pertinent data regarding the absorption, distribution, metabolism and excretion of maleic anhydride are limited. Plasma levels of maleic anhydride were determined from beagle dogs orally administered 60 mg/kg/day of the compound for 90 days. The data were analyzed by a nonlinear parameter estimation program (Braun et al., 1975). An uptake rate constant (k_a) of 3.49×10^{-3} $days^{-1}$ and an elimination rate constant (k_e) of 8.32×10^{-2} $days^{-1}$ were obtained assuming a one-compartment model. The model predicted that steady-state (99%) was reached by day 55 of the 90-day study. Degradation of maleic anhydride would involve hydrolysis to maleic acid (U.S. EPA, n.d.), which may be hydroxylated to malic acid (U.S. EPA, 1981). Maleic acid may then enter the tricarboxylic acid cycle or be excreted unchanged or in conjugated form (U.S. EPA, 1981).

5. EFFECTS

5.1. CARCINOGENICITY

Preache (1983) reported that no treatment-related increased tumor incidences were observed in Fischer 344 rats exposed to dietary maleic anhydride at doses of 10, 32 and 100 mg/kg/day for 2 years (Section 5.5.).

Dickens and Jones (1963) subcutaneously injected an unspecified number of 2-month-old male Wistar rats weighing 100 g with 1 mg maleic anhydride in arachis oil twice weekly in the right flank for 61 weeks with an additional 26-week observation period. Controls were injected repeatedly with arachis oil for 61 weeks. Two of the three rats surviving to time of first tumor (80 weeks) developed local tumors that were later determined to be fibrosarcomas capable of growth after transplantation. No local tumors were found in four controls surviving for 106 weeks. Maleic anhydride has not been scheduled for testing by the National Toxicology Program (NTP, 1985).

5.2. MUTAGENICITY

Ishidate and Yoshikawa (1980) and Ishidate et al. (1981) reported positive results for maleic anhydride (purity not specified) in a chromosome aberration test in Chinese hamster cells. Apparently, S-9 metabolic activation was used in some of the assays, but whether a positive result was also obtained with metabolic activation was not clear. Farrow and Cortina (1983) reported negative results for a bone marrow chromosome aberration assay in which rats were exposed by inhalation to maleic anhydride at 0, 1 or 100 mg/m^3 for 6 hours. Ishidate and Yoshikawa (1980) and Ishidate et al. (1981) reported negative results for maleic anhydride when tested by plate incorporation in the reverse mutation assay in Salmonella typhimurium strains TA98, TA100, TA1537 with or without metabolic (S-9) activation.

Flowers (1977) also reported negative results for maleic anhydride when tested at concentrations of 1, 10, 25, 50, 100 and 500 µg/plate in S. typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 with or without metabolic activation.

5.3. TERATOGENICITY

Groups of 25 pregnant Charles River (CD) rats were administered 0, 30, 90 and 140 mg/kg/day maleic anhydride orally in corn oil (1%) from days 6-15 of gestation (Goldenthal et al., 1979a). Fetuses were removed by Cesarean section on day 20 of gestation and were weighed, sexed and examined for external, soft tissue and skeletal anomalies and variations. Observations were recorded concerning the number of viable and nonviable fetuses, early and late resorptions, corpora lutea and total implantations. No treatment-related abnormalities in fetal development were observed at any dose level. Fetal body weights in the treated groups were lower than the controls, but this was not considered compound-related since the fetal weight of the control group was unusually high. Maternal respiratory involvement and red nasal discharge were observed in all dosage groups but was not dose-related.

As reported in abstracts, CD-1 mice were treated with intraperitoneal injections of maleic anhydride on days 8-10 or 11-13 of gestation (Dixon et al., 1978; Brown et al., 1978). Abnormalities in offspring from mice treated on days 11-13 with maleic anhydride were observed at a dose of 0.375 mmol/kg (36.8 mg/kg). Additional details were not provided.

5.4. OTHER REPRODUCTIVE EFFECTS

Jessup et al. (1982) conducted a 3-generation reproduction study using CD rats. The F_0 generation consisted of 10 male and 20 female 5- or 6-week-old rats treated by gavage with maleic anhydride in corn oil at doses of 0, 20, 55 or 150 mg/kg/day until the generation was sacrificed. The F_0 generation was mated twice to produce the F_{1a} and F_{1b} generations.

F_{1b} generation rats were similarly treated when they were 22 days old and mated to produce the F_{2a} and F_{2b} generations. First matings occurred at least 80 days after treatment began. No F_2 generation of the high-dose group was produced because there was 100% mortality of the high-dose F_{1b} females. No treatment-related effects were observed in fertility indices, litter size, pup size or pup survival. Pup growth was inhibited during lactation in the 150 mg/kg/day group.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

In an unpublished 2-year feeding study, male and female Fischer 344 rats were exposed to dietary maleic anhydride that provided intakes of 10, 32 or 100 mg/kg bw/day for 2 years (Preache, 1983). Although the number of rats in each group was not specifically reported, apparently 5 rats/sex from each group were sacrificed at 6 and 12 months, and ~20 rats/group (sex not specified) were sacrificed at 18 and 24 months. The body weights of male rats dosed at 32 and 100 mg/kg bw/day were slightly depressed compared with controls, while at the 10 mg/kg/day level, no effect on body weight or food consumption was observed. Marginal decreases in body weight were also observed in females dosed at 32 and 100 mg/kg/day compared with controls, and no effect on body weight was observed in females dosed at 10 mg/kg/day. For the first year, treated male and female rats had significantly lower food consumption, which occurred sporadically, but there was little indication of a dose-response relationship. During the first 6-12 months of the study, reduced erythrocyte counts and hematocrit were observed in treated males; however, no significant differences in the same parameters were observed after 18 and 24 months. Gross and comprehensive histopathological examination revealed no treatment-related lesions or tissue changes. No treatment-related effects on appearance, behavior, mortality, urinalysis and clinical chemistry parameters or organ weight were observed.

At least two technical problems in the study compromise the results. Adequate methods to assure that maleic anhydride added to the diet had not decomposed by the time it was fed to the rats were not used. At the time of the study, no method of analyzing feed for maleic anhydride content was available, but refrigerated or frozen samples of the feed were reserved for later testing. Since maleic anhydride hydrolyzes to maleic acid at a relative humidity >50% (Rosenfeld and Murphy, 1967), hydrolysis to maleic acid could have occurred during the 2-4 years of storage. When tested subsequently by a method developed later, the stored feed had concentrations of 69 and 75% of expected values for males and females, respectively. The concentrations observed for freshly prepared feed were 95-106% of expected values. Therefore the dosages reported probably overestimate the actual intake of maleic anhydride. In addition, lesions such as uterine adenocarcinoma, cataracts and related ophthalmological lesions occurred at unusually high incidences in treated and control rats. Preache (1983) speculated that these effects may have been the result of continuous lighting for unknown lengths of time during the first 18 months of the study, and stated that the potential influence of this problem on the results of the study is unknown.

In the 3-generation gavage study using rats conducted by Jessup et al. (1982) (see Section 5.4.), toxic effects were observed in the parental rats. High-dose (150 mg/kg/day) F_0 and F_1 parental rats had reduced body weight gain (with no effect on food consumption) and >65% mortality. Some of the deaths were attributed to gavage error, but postmortem examinations revealed that many deaths were compound-related. Scheduled sacrifices were performed on F_0 and F_{1b} parental rats after the second litters were weaned. F_{1a}, F_{2a} and F_{2b} pups were sacrificed at weaning. Gross

necropsies were performed on all rats. Comprehensive histological examinations were performed on all F_0 and F_1 parental rats that died during the study, selected F_0 parents from all groups, selected parents from the control and mid-dose (55 mg/kg/day) groups of the F_1 generation and 10 weanlings/sex from the control and mid-dose group of the F_{2b} litters. Compound-related histopathological lesions included renal corticol necrosis, hydronephrosis, chronic pyelonephritis, nephrosis, inflammation of the urinary bladder and urinary calculi in high-dose F_0 and F_1 parents that died during the study. These lesions were also observed randomly in rats that survived until sacrifice in all dosed groups of the F_0 generation and were considered to be compound-related. Inflammatory lesions in the stomach of rats of all dosed groups may have been compound-related, but this was not confirmed. There were no compound-related macroscopic or microscopic lesions in weanlings.

Three subchronic feeding studies, two in rats and one in dogs, were available. In the first study, maleic anhydride was fed to groups of 15 male and 15 female Sprague-Dawley rats at levels that provided 0, 20, 40, 100, 250 or 600 mg/kg/day (Humiston et al., 1975a). After 90 days, the rats were killed and gross and comprehensive histological examinations were performed. No effects on appearance and behavior, body weight gain and food consumption, hematological, clinical chemistry and urinalysis parameters, and no treatment-related gross or histopathological lesions were observed at 20 or 40 mg/kg/day. At $\geq$100 mg/kg/day, gross and histologically observed renal lesions (not otherwise specified) occurred in male rats. At 250 mg/kg/day, female rats had gross but not microscopic renal lesions, and male rats had increased absolute and relative kidney weights in addition to the renal lesions. At 600 mg/kg/day, both sexes had gross and microscopic renal

lesions, increased absolute and relative kidney weights and slight proteinuria, and males had increased relative liver weights. One male rat each at 250 and 600 mg/kg/day had a pulmonary adenoma.

In a subsequent study, no pulmonary adenomas were observed in groups of 75 male Sprague-Dawley rats maintained on diets providing doses of maleic anhydride of 250 or 600 mg/kg/day for 183 days (Humiston and Quast, 1977). A group of 50 male rats served as controls. The only treatment-related effects were increases in absolute and relative liver and kidney weights and renal lesions at both doses similar to those observed in the 90-day study.

In a 90-day study, groups of four male and four female beagle dogs were maintained on diets containing maleic anhydride at concentrations that provided 0, 20, 40 or 60 mg/kg/day (Humiston et al., 1975b). No treatment-related effects on appearance and behavior, body weight gain, organ weights, clinical chemistry and urinalysis parameters, and no treatment-related gross or histological lesions were observed. At 60 mg/kg/day, male dogs had equivocal decreases in packed cell volume and hemoglobin concentration determined at 83 days compared with pretreatment values.

In a 6-month inhalation study, groups of 15 male and 15 female CD rats, 15 male and 15 female hamsters, and 3 male and 3 female rhesus monkeys were exposed to vapors of maleic anhydride at concentrations of 0, 0.0011, 0.0033 and 0.010 mg/ℓ for 6 hours/day, 5 days/week for 132-136 exposures (Ulrich et al., 1981). Hematology and clinical chemistry urinalysis and opthalmoscopic tests were performed on all animals. Monkeys were also given pulmonary function tests. Upon necropsy, organ weights were recorded for all animals and tissues were obtained for comprehensive histopathologic evaluation of high-dose and control groups only.

Rats exhibited dose-related increased severity of red-tinged nasal discharge, sneezing and isolated cases of ocular irritation. No treatment-related opthalmologic effects were observed. Body weights were significantly reduced in high-dose male rats and mid- and high-dose female rats. Changes were observed in the hematology of the dosed groups; however, the values were within the normal range of variation. Brain cholinesterase levels were significantly increased in mid- and high-dose males only at 6 months. However, these values were within the expected range and were not considered treatment-related. Histopathologic evaluation of tissues from high-dose and control rats revealed no compound-related effects.

In hamsters, a number of deaths occurred, but mortality was not attributed to maleic anhydride exposure but to the stress and trauma of blood collection. High-dose animals exhibited nasal discharge, ocular irritation and some dyspnea and gasping. These effects were less severe in the low- and mid-dose levels. Body weights were not significantly changed. Hematology changes were observed but the values were within the normal range of variation. In male hamsters only, brain cholinesterase was elevated in the high-dose group at 6 months. Histopathologic examination of high-dose groups and controls revealed no compound-related effects.

High-dose monkeys exhibited nasal and ocular irritation, and slight dyspnea with coughing and sneezing. Body weights of monkeys were not reduced. Pulmonary function tests revealed no treatment-related effects in respiratory rate, tidal volume, resistance and compliance. Changes in hematology and clinical chemistry were within the normal range of variation. The red blood cell cholinesterase of high-dose female monkeys was reduced at 3 months. Histopathologic evaluation of the tissues of control and high-dose monkeys revealed no compound-related changes.

Ten male and 10 female CD rats were exposed to 0, 0.012, 0.032 and 0.086 mg/ℓ maleic anhydride vapors for 6 hours/day, 5 days/week for 21 or 22 exposures (Goldenthal et al., 1979b). Dose-related decreases in weight gain were noted in both sexes of rats at the intermediate and high levels; food consumption was decreased for the females only at these levels. Significantly higher percentages of neutrophils were observed in high-dose females and eosinophils in all high-dose rats. However, these differences were not considered physiologically relevant since the values were within the normal range.

No treatment-related effects were observed in clinical chemistry or urinalysis parameters. Gross necropsies were performed on all groups. Comprehensive histological examination was performed on controls and high-dose groups. Only the lungs, trachea and nasal turbinates were examined for the other groups. Compound-related upper respiratory lesions observed in all treatment groups included squamous metaplasia and inflammatory infiltrate in the mucosa of the trachea and nasal turbinates, epithelial hyperplasia in the nasal turbinates, and localized intraalveolar hemorrhage and presence of foamy macrophages in the alveoli. Compound-related upper respiratory and lung lesions occurring only in the high and intermediate dosage groups included dark red lung foci, adhesions, congestion, hemorrhage and localized atelectasis in the lungs, bronchial epithelial hyperplasia and squamous metaplasia, and hyperplasia of the tracheal epithelium. Keratitis or corneal vascularization was also observed in high-dose rats.

Grigor'yeva (1966) exposed groups of 10 male white rats (90-120 g) by inhalation to 0.0, 0.03, 0.08, 0.34 and 0.8 mg/m^3 continuously for 70 days. The actual concentration of maleic anhydride fluctuated widely at all levels. At 0.34 and 0.8 mg/m^3, overall condition and weight changes

(particularly affected during a period of experimental starvation) were affected, leukocytosis was observed and phagocytic activity of neutrophils was decreased compared with controls. At 0.8 mg/m^3, the number of erythrocytes declined, protein sulfhydryl groups were blocked, and atrophy of nasal mucosa and lung inflammation was observed.

Several reports concerning the human health effects of maleic anhydride were located in the available literature. The respiratory organs, skin and eyes appear to be sensitive to the adverse effects of maleic anhydride exposure. Workers who were chronically exposed to maleic anhydride had chronic bronchitis more frequently than workers exposed to phthalic anhydride (ACGIH, 1986). Repeated exposure may result in asthma-like attacks and dermatitis (U.S. EPA, n.d., 1981). Maleic anhydride is considered to be a sensitizer of the skin (ACGIH, 1984).

Grigor'yeva (1966) reviewed a study that reported that humans exposed to a mixture of chemicals (maleic anhydride, phthalic anhydride, napthoquinone and carbon monoxide) for 20 months had a decrement in general health. Signs and symptoms included nervous system disorders (fits of excitation, tetanic state, sensitivity impairment in the area of the trigeminal nerve); hypersecretion in the stomach; increased permeability of stomach and vessel walls; decreased diastolic and systolic pressure; conjunctivitis; nasal hemorrhages; ulcerations of the larynx, pharynx, trachea and bronchi; blood changes; decreased vitamin C and impairment of phosphorus and calcium metabolism.

5.6. OTHER RELEVANT INFORMATION

The acute toxicity of maleic anhydride is summarized in Table 5-1. There is some interspecies variation in LD_{50}s, but most values differ by a factor of 2.

TABLE 5-1

Acute Toxicity of Maleic Anhydride

Route	Species	LD_{50} (mg/kg)	Reference
Oral	rat	481	Marhold, 1977
Oral	rat	850	Berzins, 1967
Oral	rat (M)	409	Lichy et al., 1975
Oral	rat (F)	235	Lichy et al., 1975
Oral	rat	1050	Younger Laboratories, 1976
Oral	rat	900	Younger Laboratories, 1976
Oral	mouse	465	Berzins, 1967
Oral	guinea pig	390	Berzins, 1967
Oral	rabbit	875	Berzins, 1967
Dermal	rabbit	2620	Vernot et al., 1977

Kryzhanovskaya (1969) found that maleic anhydride used as an allergenic substance caused bronchial asthma in guinea pigs after ≥14-21 days of inhalation exposure. Kryzhanovskaya (1970) also reported that maleic anhydride inhaled by animals (species, unspecified) at levels of 5.0×10^{-8} to 5.0×10^{-5} mg/m³ showed an "allergenic action." Unspecified toxic effects were noted at 0.5-50 mg/m³. Berzins (1967) reported no "accumulative" effect in rats given 85 mg/kg orally for 20 days.

U.S. EPA (1980a) reported that a mixture of chemicals (75% diallyl diglycol carbonate, 20% maleic anhydride, 5% tungsten hexacarbonyl and 100 ppm hydroquinone monomethyl ether) applied to the eyes of rabbits caused clouding of the cornea within 20 seconds. Rinsing for 1 minute had no effect on the condition, and the cloudiness and ulcers were evident after 14 days. These effects were considered immediate and irreversible. Maleic anhydride was considered the most likely chemical in the mixture to cause such damage.

Greigor'yeva (1966) reported the results of a series of experiments in which human subjects were exposed acutely to maleic anhydride by inhalation. Subjects exposed to 8-11 mg/m³ (dosing schedules not reported for any concentration) had burning in the larynx, reflex cough and lacrimation. At exposures of 5-7 mg/m³, the subjects experienced irritation of the respiratory tract; at 2-3 mg/m³, effects were insignificant and slightly irritating. The threshold of dryness and tickling in the pharynx was 1.0 mg/m³. Three subjects were tested for reflex changes in light sensitivity of the eye, which were considered to be indicative of change in the cerebral cortex. A change in light sensitivity of the eye was observed (compared with controls) after a 20-minute exposure to 1.65 and 6.2 mg/m³, but not at 0.85 mg/m³. Grigor'yeva (1960) suggested that 0.25-0.38 ppm (1.0-1.5

mg/m³) was the minimal amount of maleic anhydride that caused conjunctival and upper respiratory tract irritation; whereas, 0.22 ppm (0.88 mg/m³) was ineffective. In a preliminary evaluation (which may be based on incomplete information), U.S. EPA (1978) reported that occupational exposure to maleic anhydride may lead to irritation in the respiratory tract and eyes.

ACGIH (1986) reported that exposure to 1.5-2.0 ppm (1.0-8.0 mg/m³) maleic anhydride for 15 minutes caused eye irritation, and that continued exposure may result in chronic eye irritation and keratitis. McLaughlin (1946) reported 14 cases of corneal burns attributable to maleic anhydride exposure. Apparently, these burns healed promptly (48 hours).

5.7. SUMMARY

The carcinogenicity of maleic anhydride has not been adequately tested nor has it been scheduled for testing by the National Toxicology Program (NTP, 1986). Preache (1983) observed no treatment-related increase in tumorigenesis in rats given dietary maleic anhydride at concentrations providing doses of 0, 10, 32 and 100 mg/kg/day for 2 years. Inadequate evidence of carcinogenicity was provided by Dickens and Jones (1963) who observed local fibrosarcomas in rats subcutaneously injected with maleic anhydride. Maleic anhydride was positive in the chromosomal aberration test in Chinese hamster cells without activation, but negative for chromosome aberrations in the bone marrow of rats exposed by inhalation (Farrow and Cortina, 1983) and negative in the Salmonella typhimurium reverse mutation test with and without metabolic activation (Ishidate and Yoshikawa, 1981; Ishidate et al., 1981; Flowers, 1977). No teratogenic or fetotoxic effects were observed in the offspring of CD rats treated by gavage with maleic anhydride at ≤140 mg/kg/day during gestation (Goldenthal et al., 1979a).

In mice, an intraperitoneal dose of 36.8 mg/kg on days 11-13 of gestation appeared to be a threshold associated with malformation in the offspring (Dixon et al., 1978; Brown et al., 1978). No effects on reproductive indices were observed in rats treated by gavage with 20, 55 or 150 mg/kg/day for three generations (Jessup et al., 1982).

The chronic toxicity of maleic anhydride has not been adequately studied. Preache (1983) fed rats diets providing doses of 0, 10, 32 or 100 mg/kg/day. At 32 and 100 mg/kg/day, male rats had a dose-related but slight (<6%) decrease in body weights which was statistically significant. A marginal decrease in body weight accompanied by decreased food consumption was also observed in female rats at 32 and 100 mg/kg/day. Since decreased food consumption was also reported at sporadic intervals in these groups, the biological significance of these observations is questionable. Because the maleic anhydride in the stored feed hydrolyzed to maleic acid, the doses were probably overestimated.

In the 3-generation study, compound-related mortality and renal pathology occurred in F_0 and F_1 parent rats treated by gavage with 150 mg/kg/day (Jessup et al., 1982). In rats that survived until sacrifice, renal lesions occurred randomly in F_0 rats treated at 20, 55 and 150 mg/kg/day and were considered compound-related.

In subchronic feeding studies, no effects were observed in rats given $\leq$40 mg/kg/day for 90 days (Humiston et al., 1975a). At $\geq$100 mg/kg/day, there were gross and histopathological renal lesions, at $\geq$250 mg/kg/day, increased kidney weights and at 600 mg/kg/day, increased liver weights and proteinuria. The only effects in dogs given 20, 40 or 60 mg/kg/day in the diet for 90 days were equivocal decreases in packed cell volume and hemoglobin concentration in only male dogs at 60 mg/kg (Humiston et al., 1975b).

Acute oral LD_{50} values range from 390-875 mg/kg in guinea pigs, mice, rats and rabbits (Marhold, 1977; Berzins, 1967).

Inhalation exposure to maleic anhydride vapor at 0.0011, 0.0033 and 0.010 mg/ℓ, 6 hours/day, 5 days/week for 6 months resulted in dose-related increased severity of nasal and ocular irritation in rats and hamsters at all concentrations and monkeys at the high concentration (Ulrich et al., 1981). Rats at 0.0033 and 0.01 mg/ℓ also had reduced body weights. In rats exposed by inhalation to $\geq$0.012 mg/ℓ, 6 hours/day, 5 days/week for 4 weeks, upper respiratory and lung squamous metaplasia, inflammatory infiltrate, hyperplasia and hemorrhage were observed (Goldenthal et al., 1979b).

Occupational exposure of humans to maleic anhydride has been associated with skin sensitization, chronic bronchitis, asthma, pulmonary edema, upper respiratory tract irritation and corneal burns (U.S. EPA, n.d., 1981; Grigor'yeva, 1966; ACGIH, 1986). Exposures to 1.0-8.0 mg/m^3 for 15 minutes may cause eye irritation and continued exposure may result in chronic eye irritation and keratitis (ACGIH, 1986).

6. AQUATIC TOXICITY

6.1. ACUTE

Limited information is available concerning the acute toxicity of maleic anhydride to fishes. Lysak and Marcinek (1972) reported that 165 mg/ℓ caused no mortality of rainbow trout, Salmo gairdneri, in 48 hours, while 260 mg/ℓ caused 100% mortality in 24 hours. Cohle and McAllister (1982a) determined 96-hour LC_{50} and NOEL values of 75 and 32 mg/ℓ, respectively, for rainbow trout. Wallen et al. (1957) determined 24-, 48- and 96-hour LC_{50} values of 240, 240 and 230 mg/ℓ, respectively for mosquitofish, Gambusia affinis. All fish survived concentrations of ≤180 mg/ℓ for 96 hours, and 320 mg/ℓ caused 100% mortality in 24 hours. Turnbull et al. (1954) reported 24-hour LC_{50} values of 150 and 165 mg/ℓ and 48-hour LC_{50} values of 138 and 145 mg/ℓ for the bluegill, Lepomis macrochirus. These authors calculated "safe" concentrations of 34 and 35 mg/ℓ using the formula: safe concentration = 24-hour LC_{50} x 0.3/(24-hour LC_{50}/48-hour LC_{50})[a]. Cohle and McAllister (1982b) determined 96-hour LC_{50} and NOEL values of 75 and 56 mg/ℓ, respectively, for bluegills. Knie et al. (1983) determined LC_0, LC_{50} and LC_{100} values of 100, 115 and 125 mg/ℓ maleic anhydride for the golden orfe, Leuciscus idus.

Limited data are available concerning effects of maleic anhydride on aquatic invertebrates. Bringmann and Kuehn (1982) determined effective concentrations for immobilization of Daphnia magna. The 24-hour EC_0, EC_{50} and EC_{100} values were 63, 88 and 125 mg/ℓ, respectively; however, when the experiment was repeated and the pH of the test solutions was neutralized, the EC_0, EC_{50} and EC_{100} values were much higher (3950, 5600 and 6364 mg/ℓ, respectively), indicating that the toxicity of maleic anhydride to Daphnia magna is due to acidification of the test medium.

Forbis (1982) determined 48-hour LC_{50} and NOEL values of 330 and 180 mg/ℓ, respectively, for Daphnia magna. He noted that pH decreased with increasing maleic anhydride concentration, but it was still within acceptable limits at the test concentration closest to the eventual LC_{50} value (i.e., pH was 7.0 at 320 mg/ℓ maleic anhydride).

6.2. CHRONIC

Pertinent data regarding chronic toxicity of maleic anhydride to aquatic organisms could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

Knie et al. (1983) reported an EC_{50} of 190 mg/ℓ for inhibition of oxygen production in the alga, Haematococcus pluvialis, and an EC_{10} of 63 mg/ℓ for inhibition of oxygen consumption by the bacterium, Pseudomonas putida.

6.4. RESIDUES

Pertinent data regarding maleic anhydride residues in aquatic biota could not be located in the available literature as cited in the Appendix.

6.5. SUMMARY

The limited information available indicates that maleic anhydride is acutely toxic to fish and aquatic invertebrates at concentrations of $\geq$56 mg/ℓ. LC_{50} values for fish range from 75 mg/ℓ for bluegills and rainbow trout to 240 mg/ℓ for mosquitofish (Cohle and McAllister, 1982a,b; Turnbull et al., 1954; Wallen et al., 1957). The EC_{50} for immobilization of Daphnia magna is 88 mg/ℓ (Bringmann and Kuehn, 1982). No toxic effects were reported in any species at concentrations <50 mg/ℓ. Pertinent data regarding the chronic toxicity or accumulation of maleic anhydride in aquatic organisms could not be located in the available literature as cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

ACGIH (1986) adopted a TLV of 0.25 ppm (1 mg/m^3) for maleic anhydride. The TLV was recommended to provide protection against respiratory irritation in nonsensitized workers (ACGIH, 1986). The OSHA standard for maleic anhydride is also 1 mg/m^3 (CFR, 1985).

7.2. AQUATIC

Pertinent data regarding aquatic guidelines and standards for maleic anhydride could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

The carcinogenicity of maleic anhydride has not been adequately tested nor has it been scheduled for testing by the National Toxicology Program (NTP, 1986). Preache (1983) observed no treatment-related increase in tumorigenesis in rats given dietary maleic anhydride at doses of 0, 10, 32 and 100 mg/kg/day for 2 years. Because the maleic anhydride in the stored feed hydrolyzed to maleic acid, these doses are probably overestimated. Inadequate evidence of carcinogenicity was provided by Dickens and Jones (1963) who observed local fibrosarcomas in rats subcutaneously injected with maleic anhydride. Maleic anhydride was positive in the chromosomal aberration test in Chinese hamster cells without metabolic activation, but negative for chromosome aberrations in the bone marrow of rats exposed by inhalation (Farrow and Cortina, 1983; Ishidate and Yoshikawa, 1980; Ishidate et al., 1981; Flowers, 1977), but was negative in the Salmonella typhimurium reverse mutation test with and without activation (Ishidate and Yoshikawa, 1981; Ishidate et al., 1981). No teratogenic or fetotoxic effects were observed in the offspring of CD rats treated with maleic anhydride by gavage at $\leq$140 mg/kg/day during gestation (Goldenthal et al., 1979a). In mice, an intraperitoneal dose of 36.8 mg/kg on days 11-13 of gestation appeared to be a threshold associated with malformation in the offspring (Dixon et al., 1978; Brown et al., 1978). No effects were observed on reproductive indices in rats treated by gavage with 20, 55 or 150 mg/kg/day for three generations (Jessup et al., 1982).

The chronic toxicity of maleic anhydride has not been adequately studied. Preache (1983) fed rats concentrations of 0, 10, 32 or 100 mg/kg/day.

No adverse effects were noted at any treatment levels attributable to exposure to maleic anhydride. At 32 and 100 mg/kg/day, male rats had a dose-related but slight (<6%) decrease in body weight which was statistically significant. A marginal decrease in body weight accompanied by decreased food consumption was also observed in female rats at 32 and 100 mg/kg/day. Since decreased food consumption was also reported at sporadic intervals in these groups, the biological significance of these observations is questionable. The reliability of the Preache (1983) study should be questioned, however, because the actual content of maleic anhydride in the diets consumed by the rats is unknown. Analysis of preserved aliquots of these diets 2-4 years after they were fed indicated a recovery of 69-75% of expected levels. Analysis of freshly prepared diets yielded recoveries of 95-106% of the incorporated material. Although during the experiment the test diets were prepared weekly, the rate of degradation of maleic anhydride in rat diet is not known; however, the actual dietary content consumed by the rats was probably at least 70-75% of the target doses.

In the 3-generation study, compound-related mortality and renal pathology occurred in F_0 and F_1 parent rats treated by gavage with 150 mg/kg/day (Jessup et al., 1982). In rats that survived until sacrifice, renal lesions occurred randomly in F_0 rats treated at 20, 55 and 150 mg/kg/day and were considered compound-related.

In a 90-day feeding study using rats, however, doses $\geq$100 mg/kg/day resulted in unspecified kidney lesions (Humiston et al., 1975a). At $\geq$250 mg/kg/day, the rats had increased absolute and relative kidney weights, and at 600 mg/kg/day, increased absolute and relative liver weights and proteinuria were also observed. No effects were observed at $\leq$40 mg/kg/day.

The only effects observed in dogs fed diets providing 20, 40 or 60 mg/kg/day for 90 days were equivocal decreased packed cell volume and hemoglobin concentration at 60 mg/kg/day (Humiston et al., 1975b). The results of analyses of the dietary content of maleic anhydride in the Humiston et al. (1975a,b) studies are unknown.

Inhalation exposure to maleic anhydride vapor at 0.0011, 0.0033 and 0.010 mg/ℓ, 6 hours/day, 5 days/week for 6 months resulted in dose-related increased severity of nasal and ocular irritation in rats and hamsters at all concentrations and monkeys at the high concentration (Ulrich et al., 1981). Rats at 0.0033 and 0.01 mg/ℓ also had reduced body weights. In rats exposed by inhalation to $\geq$0.012 mg/ℓ, 6 hours/day, 5 days/week for 4 weeks, upper respiratory and lung squamous metaplasia, inflammatory infiltrate, hyperplasia and hemorrhage were observed (Goldenthal et al., 1979b). Thus, there are sufficient data from oral studies to derive an ADI for oral exposure.

Although the nominal 100 mg/kg/day level in the 2-year study appeared to be the highest chronic NOAEL from the Humiston et al. (1975a) study, the finding of renal lesions in rats fed a nominal dose of 100 mg/kg/day for 90 days and 20 mg/kg/day in the 3-generation study indicates that the lower nominal dose of 10 mg/kg/day in the 2-year study should more appropriately be considered the NOAEL for chronic exposure since it is the dose level that falls below the other LOAELs. Dividing the NOAEL of 10 mg/kg/day by an uncertainty factor of 100 results in an ADI of 0.10 mg/kg/day or 7.0 mg/day for a 70 kg human. The ADI is now most often referred to as the Reference dose (RfD). Maleic anhydride, however, has not been adequately tested for carcinogenicity.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The available chronic or subchronic studies of maleic anhydride were discussed in Section 5.5. and are summarized in Table 9-1. Maleic anhydride in the diet hydrolyzes to maleic acid; therefore, the nominal oral doses reported in Table 9-1 are probably overestimated. For inhalation exposures, transformed doses were calculated by expanding the exposures to continuous, by multiplying the animal inhalation rate and dividing by the animal body weight. For rats, inhalation rates were calculated according to the method described by U.S. EPA (1980b). For hamsters and monkeys, inhalation rates were calculated by the method described by U.S. EPA (1985b). Equivalent human doses were calculated by multiplying the animal dose by the cube root of the ratio of the animal body weight to the reference human body weight of 70 kg. Data used to calculate the MEDs and CSs and are summarized in Table 9-2.

As seen from Table 9-1, the effects of long-term oral exposure to maleic anhydride include decreased body weight gain, renal lesions and increased mortality. Effects of inhalation exposure ranged from respiratory irritation to severe lesions and functional impairment of the lungs and from ocular irritation to corneal vascularization and keratitis. Some hematological effects were also observed.

Of the effects of oral exposure, the most severe is the increased mortality that occurred in rats treated at 150 mg/kg/day, or an equivalent human dose of 25.6 mg/kg/day for two generations (Jessup et al., 1982). Multiplying the equivalent dose by 70 kg results in an MED of 1792 mg/day, which corresponds to an RV_d of 1. Increased mortality warrants an RV_e of 10. Multiplying the RV_d by the RV_e results in a CS of 10, which corresponds to an RQ of 1000 (see Table 9-2).

TABLE 9-1

Oral Toxicity Summary for Maleic Anhydride[a]

Route	Species/ Strain	Sex	No. at Start	Average Weight (kg)	Vehicle/ Physical State	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Response	Reference
Oral	rat/ Fischer 344	M,F	~30/sex	0.40 (M)[b] 0.22 (F)[b]	diet	32 mg/kg/day for 2 years	32	5.7 (M) 4.9 (F)	Slight dose-related decreased body weight in male rats, accompanied by decreased food consumption; marginal decreased body weight in female rats accompanied by decreased food consumption	Preache, 1983
Oral	rat/ Sprague-Dawley	M,F	15/sex/ group	0.35[c]	diet	100, 250 or 600 mg/kg/day for 90 days	100, 250 or 600	17.1, 42.7 or 102.6	Gross and histologically observed renal lesions in males at ≥100 mg/kg/day; gross kidney lesions in females and increased relative and absolute kidney weight in males at 250 mg/kg/day; gross and microscopic kidney lesions and increased absolute and relative kidney weights of both sexes, increased relative liver weight of males at 600 mg/kg/day	Humiston et al., 1975a
Oral	rat/ Sprague-Dawley	M	75/group	0.35[c]	diet	250 or 600 mg/kg/day for 183 days	250 or 600	42.7 or 102.6	Kidney lesions and organ weight changes similar to those observed in 90-day study	Humiston and Quast, 1977
Oral	rat/CD	M,F	10 or 20/ group	0.35[c]	corn oil	20, 55 or 150 mg/kg/day for 2 or 3 generations	20, 55 or 150	3.4, 9.4 or 25.6	Increased mortality of 150 mg/kg/day parents, histopathological renal lesions; renal cortical necrosis, hydronephrosis, nephrosis, calculi in parents at all doses	Jessup et al., 1982

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TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	No. at Start	Average Weight (kg)	Vehicle/ Physical State	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Response	Reference
Oral	dog/ beagle	M	4	12.7[d]	diet	60 mg/kg/day for 90 days	60	34.0	Equivocal decreased packed cell volume and hemoglobin concentration	Humiston et al., 1975b
Inhalation	rat/CD	M,F	15/sex/ group	0.43 (M)[b] 0.29 (F)[b]	air/vapor	0.0011, 0.0033 or 0.010 mg/ℓ, 6 hours/day, 5 days/week, 6 months	0.12 (M), 0.13 (F) 0.35 (M), 0.40 (F) 1.1 (M), 1.2 (F)	0.02 (M,F) 0.06 (M,F) 0.20 (M), 0.19 (F)	Respiratory and ocular irritation at all exposures, reduced body weight gain in mid-dose females and high-dose males and females	Ulrich et al., 1981
Inhalation	rat/CD	M,F	10/sex/ group	0.30 (M)[b] 0.20 (F)[b]	air/vapor	0.012, 0.032 or 0.086 mg/ℓ, 6 hours/day, 5 days/week for 4 weeks	1.4 (M), 1.7 (F) 3.8 (M), 4.4 (F) 10.3 (M), 11.8 (F)	0.23 (M), 0.24 (F) 0.62 (M,F) 1.7 (M,F)	Decreased body weight at mid- and high-dose levels for both sexes; squamous metaplasia and inflammatory infiltrate, hyperplasia, localized hemorrhage in upper respiratory tract at ≥0.012 mg/ℓ; adhesions, congestions, hemorrhage, atelectasis in lungs, hyperplasia and squamous metaplasia of bronchiolar epithelium at ≥0.032 mg/ℓ; keratitis and corneal vascularization at 0.086 mg/ℓ	Goldenthal et al., 1979b
Inhalation	rat/NR	M	10/group	0.35[c]	air/vapor	0.34 or 0.8 mg/m³ continuous for 70 days	0.22 or 0.51	0.04 or 0.09	Leukocytosis and decreased phagocytic activity of neutrophils at both exposures; decreased erythrocytes, atrophy of nasal mucosa and lung inflammation at 0.8 mg/m³	Grigor'yeva, 1966

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TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	No. at Start	Average Weight (kg)	Vehicle/ Physical State	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Response	Reference
Inhalation	hamster/ NR	M,F	15/sex/ group	0.105[b] (M,F)	air/vapor	0.0011, 0.0033 or 0.010 mg/ℓ, 6 hours/day, 5 days/week for 6 months	0.19, 0.56 or 1.7	0.02, 0.06 or 0.19	Respira'ory and ocular irritation at all exposures	Ulrich et al., 1981
Inhalation	monkey/ rhesus	M,F	3/sex/ group	4 (M)[b] 3 (F)[b]	air/vapor	0.010 mg/ℓ 6 hours/day, 5 days/week for 6 months	0.92 (M) 0.82 (F)	0.35 (M) 0.29 (F)	Respiratory and ocular irritation, coughing, dyspnea	Ulrich et al., 1981

[a]Purity not reported

[b]Estimated from growth curves in the report

[c]Reference rat body weight as recommended by U.S. EPA, 1980b

[d]Reference dog body weight as recommended by U.S. EPA,, 1985b

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TABLE 9-2

Composite Scores for Maleic Anhydride in Rats

Route	Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Oral	150	1792	1.0	Increased mortality	10	10	1000	Jessup et al., 1982
Oral	20	238	1.9	Renal cortical necrosis, hydronephrosis, nephrosis, calculi	7	13.3	1000	Jessup et al., 1982
Inhalation	3.8	43.4	3.0	Lung lesions; adhesions, congestion, hemorrhage, atelectasis, hyperplasia, squamous metaplasia	8	24	100	Goldenthal et al., 1979b
Inhalation	1.4	16.1	3.7	Squamous metaplasia and hyperplasia, hemorrhage in upper respiratory tract	7	25.9	100	Goldenthal et al., 1979b
Inhalation	0.35	4.2	4.6	Reduced body weight gain	4	18.4	1000	Ulrich et al., 1981
Inhalation	0.12	1.4	5.3	Ocular and respiratory irritation	2	10.6	1000	Ulrich et al., 1981
Inhalation	0.51	6.3	4.3	Nasal mucosa atrophy	3	12.9	1000	Grigor'yeva, 1966
Inhalation	0.22	2.8	4.8	Hematological effects	2	9.6	1000	Grigor'yeva, 1966

Severe histopathological renal lesions also occurred in two generations of parental rats treated at ≥20 mg/kg/day or at equivalent doses ≥3.4 mg/kg/day. Multiplying by 70 kg results in an MED of 238 mg/day, which corresponds to an RV_d of 1.9. The severity of the lesions warrants an RV_e of 7. The CS of 13.3 corresponds to an RQ of 1000.

Decreased body weight occurred after oral dosing with equivalent human doses of 4.9 and 5.7 mg/kg/day; however, since this effect is considerably less severe than renal lesions and occurred at higher doses, a CS need not be calculated.

Severe respiratory lesions (adhesions, congestion, hemorrhage, atelectasis in the lungs; hyperplasia and metaplasia of the bronchiolar epithelium) occurred at inhalation exposures equivalent to animal doses ≥3.8 mg/kg/day or human doses ≥0.62 mg/kg/day in the 4-week inhalation study by Goldenthal et al. (1979b). Although the study was relatively short-term, it is not necessary to divide the dose by an uncertainty factor of 10 because effects of similar severity were not observed at 10-fold lower exposures in a 6-month study. Multiplying the dose of 0.62 mg/kg/day by 70 kg yields an MED of 43.4, which corresponds to an RV_d of 3.0. The severity of the lung lesions warrants an RV_e of 8. The CS of 24 corresponds to an RQ of 100.

Keratitis and vascularization, which would warrant a lower RV_e, occurred at a higher concentration; therefore, a CS for these effects need not be calculated.

Similar respiratory lesions occurred in the trachea and nasal turbinates at equivalent human doses of ≥0.23 mg/kg/day in the 4-week inhalation study by Goldenthal et al. (1979b). The MED of 16.1 mg/day corresponds to an RV_d of 3.7. Since the lesions occurred in the upper respiratory tract,

they are considered to be less severe than those in the lung, and warrant an RV_e of 7. Multiplying the RV_d by the RV_e results in a CS of 25.9, corresponding to an RQ of 100.

Minor effects were observed at very low equivalent human doses in inhalation studies. Ulrich et al. (1981) reported reduced body weight gain (RV_e=4) at $\geq$0.06 mg/kg/day in rats, and respiratory and ocular irritation (RV_e=2) in rats and hamsters at $\geq$0.02 mg/kg/day in a 6-month inhalation study. Atrophy of nasal mucosa (RV_e=3) at 0.09 mg/kg/day and minor hematological effects (RV_e=2) at 0.04 mg/kg/day occurred in the Grigor'yeva (1966) inhalation study. The corresponding MEDs, RV_ds, CSs and RQs are presented in Table 9-2.

As seen from Table 9-2, the highest CS of 25.9 resulted from the data for severe upper respiratory tract lesions in rats in the study by Goldenthal et al. (1979b) and is recommended as the basis of the RQ (Table 9-3).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Maleic anhydride is not scheduled for testing by the National Toxicology Program (NTP, 1986). No treatment-related increased incidences of tumors were observed in rats maintained on diets that provided maleic anhydride at nominal doses of $\leq$100 mg/kg/day for 2 years (Preache, 1983).

Dickens and Jones (1963) subcutaneously injected an unspecified number of 2-month-old male Wistar rats with 1 mg maleic anhydride in arachis oil 2 days/week for 61 weeks and observed them for an additional 26 weeks. Controls were injected with arachis oil only. Two of the three rats surviving to the time that the first tumor appeared (80 weeks) developed local fibrosarcomas that were capable of growth after transplantation. No local tumors were found in the four control rats surviving for 106 weeks.

TABLE 9-3

Maleic Anhydride

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*:	4.2 mg/day
Effect:	histopathological lesions in respiratory tract
Reference:	Goldenthal et al., 1979b
RV_d:	3.7
RV_e:	7
Composite Score:	25.9
RQ:	100

*Equivalent human dose

These data provide inadequate evidence of maleic anhydride's carcinogenic potential in rats, and are inadequate for calculating an F factor. No data regarding the carcinogenic potential of exposure to maleic anhydride for humans were located. Therefore, maleic anhydride is appropriately placed in IARC Group 3 and CAG Group D (U.S. EPA, 1984).

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Van Wagenen, H.D. 1984. Occupational hazard control options for chemical process unit operations at Monsanto Company, Pensacola, Florida. NTIS PB84-241942. [CA 102(20):171925j]

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Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., New York.

Wallen, I.E., W.C. Greer and R. Lasater. 1957. Toxicity to Gambusia affinis of certain pure chemicals in turbid waters. Sewage Ind. Wastes. 29(6): 695-711.

Weber, R.C., P.A. Parker and M. Bowser. 1981. Vapor pressure distribution of selected organic chemicals. U.S. EPA, Cincinnati, OH. EPA-600/2-81-021.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ. p. 814.

Younger Laboratories. 1976. Toxicological investigation of maleic anhydride. Conducted for Monsanto Co., St. Louis, MO. Unpublished 8D submission. Microfiche No. OTS 0206655. Document ID 878214769.

APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN Internation
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1985-1986. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1986. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, N.I. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1985. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1985. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.